# Synopsis

The thesis entitled "***Metal-Mediated and Metal-Free Organic Transformations: C-H Functionalization of Tertiary Amines, Synthesis of Carbonyl Compounds and Ring-Opening of Aziridines"*** is presented in four chapters.

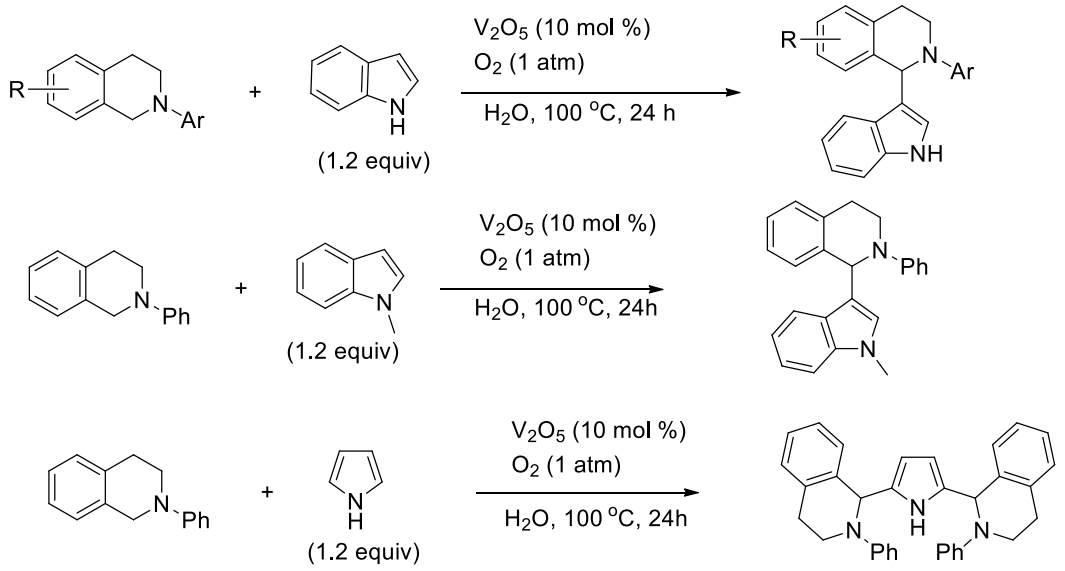
Direct activation of C-H bonds to form C-C or C-X bond is limelight in recent years among synthetic organic chemists. In this context, cross-dehydrogenative coupling (CDC) method provides an easy access to C-H functionalization of $sp^3$ C-H bonds under oxidative condition to synthesis complex natural and unnatural products from small molecules.[1] In this context, we are presenting CDC reactions to accomplish C-C bonds as well as C-P bonds in Chapter 1 and 2 that are catalyzed by metal and non-metal reagents. Besides, catalytic oxidation of organic compounds to carbonyl compounds, which is one fundamental transformation in organic chemistry,[2] is accomplished using vanadium reagent.[2] In the last chapter, our investigation on the ring-opening of aziridines with dithiocarbamates to provide nitrogen-containing molecules is presented.[3]

**Chapter 1** reveals C-H functionalization of tertiary amines by cross-dehydrogenative coupling (CDC) method mediated by transition metals under aerobic condition. This method involves direct coupling of tertiary amines with various nucleophiles, interestingly it does not require prefunctionalized starting materials for coupling reaction. Therefore, CDC reactions provide shorter synthetic routes to the required product and are more economically viable method.[1]

**Chapter 1: Part 1: An oxidative cross-dehydrogenative-coupling reaction in water using molecular oxygen as the oxidant: vanadium catalyzed indolation of tetrahydroisoquinolines**

In this chapter, we have reported an aerobic oxidative cross-dehydrogenative coupling reaction between $sp^3$ C–H and $sp^2$ C–H bonds by employing a vanadium catalyst ($V_2O_5$) in an aqueous medium using molecular oxygen as the oxidant. This environmentally benign method of indolation of *N*-aryl tetrahydroisoquinolines employs easily available and inexpensive $V_2O_5$ (10 mol %) as the catalyst is performed in aqueous medium under aerobic condition. This CDC method activates the C-H bond adjacent to tertiary nitrogen to form iminium ion intermediate and further reaction with various substituted indoles furnishes the indolyl-*N*-aryl tetrahydroisoquinolines in excellent yields. This strategy exhibits larger substrate scope and shows high regioselectivity.[4] This methodology is then extended using *N*-methylindole and pyrrole as the nucleophiles.

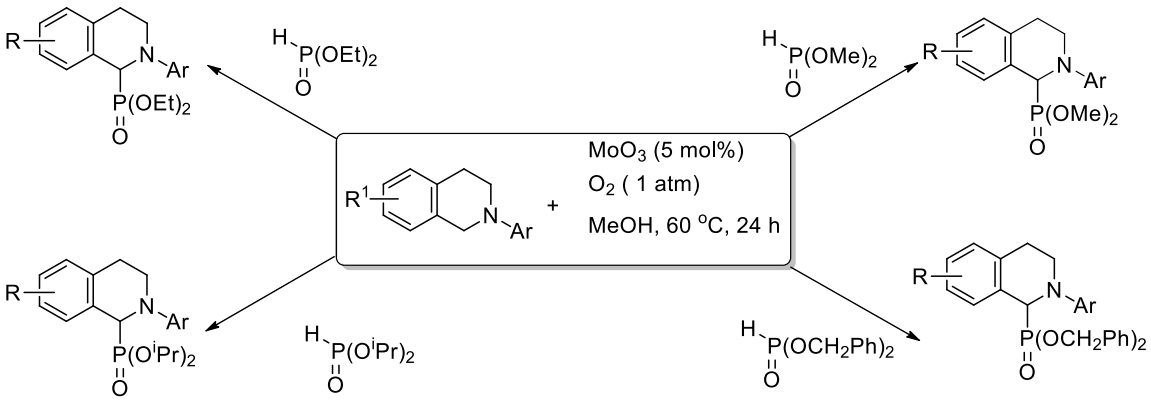
***Scheme 1.*** **Vanadium catalyzed indolation of tetrahydroisoquinolines**




**Chapter 1: Part 2: Molybdenum catalyzed oxidative cross dehydrogenative coupling of sp$^3$ C-H bonds: Synthesis of *α*-aminophosphonates under aerobic condition**

In this chapter, we describe molybdenum-catalyzed *α*-phosphonation of *N*- aryl tetrahydroisoquinolines by CDC method. Unlike other known methods, this C-P bond forming reaction employs 1.1 equiv of dialkyl-H-phosphonate by using $MoO_3$ (5 mol %) as the catalyst under aerobic condition. Further, hydrophosphorylation reaction works well with various dialkyl-H-phosphonates. Interestingly, sterically hindered phosphites such as diisopropyl phosphite and dibenzyl phosphite undergo facile coupling reaction with *N*-aryl tetrahydroisoquinolines and furnish products in excellent yields. *N*-aryl tetrahydroisoquinolines are activated to iminium ion intermediate under reaction condition and further reaction with various dialkyl phosphites furnishes the corresponding *α*-aminophosphonates.[5]

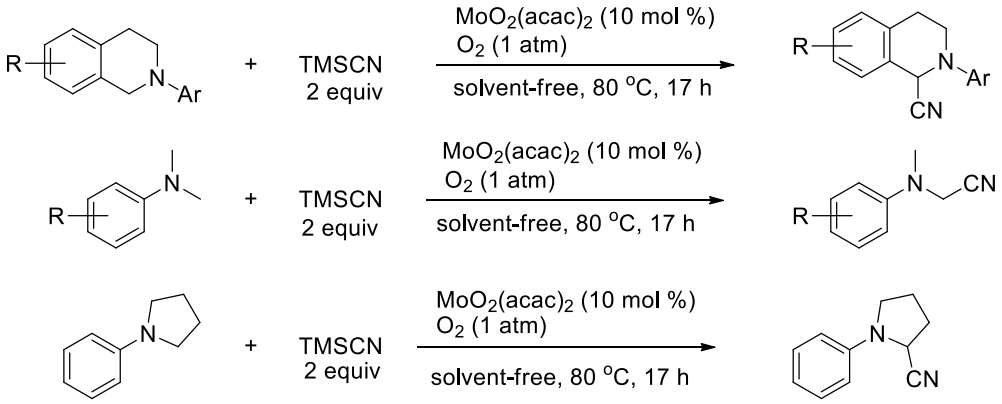
***Scheme 2.*** **Molybdenum catalyzed oxidative cross dehydrogenative coupling to synthesiss *α*-aminophosphonates under aerobic condition**



**Chapter 1: Part 3: Solvent-free synthesis of *α*-amino nitriles: A CDC approach for the cyanation of tertiary amines under aerobic condition.**

In this chapter we have demonstrated molybdenum catalyzed solvent-free synthesis of *α* -amino nitriles by oxidative cross-dehydrogenative coupling reaction under aerobic condition. This environmentally benign strategy employs catalytic amount of molybdenum (VI) acetylacetonoate ($MoO_2(acac)_2$) as the catalyst and trimethylsilylcyanide (TMSCN) as a cyanide source under solvent-free condition using molecular oxygen as the oxidant. This methodology works well with *N*-aryl tetrahydroisoquinolines, and other acyclic and cyclic tertiary amines such as *N,N*-dimethylanilines and *N*-phenyl pyrrolidine. We belive that this reaction goes through iminium ion intermediate, which undergo further coupling with cyanide ion to furnish *α*-amino nitriles. Unlike other methods, this mild strategy is performed under greener reaction condition such as acid-free, solvent-free condition.[6]

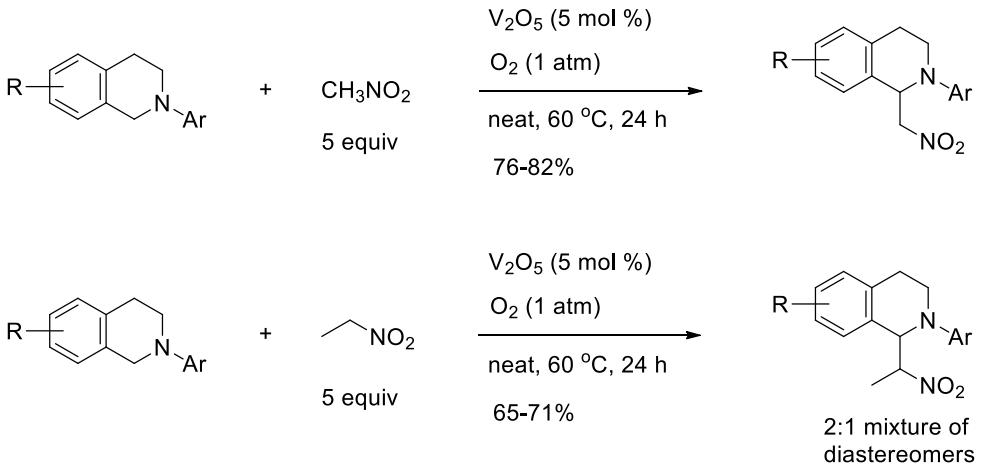
***Scheme 3.*** **CDC approach for the cyanation of tertiary amines under aerobic condition**




**Chapter 1: Part 4: Cross-dehydrogenative coupling reaction between $sp^3$ C-H bond and $sp^3$ C-H bond: Aza-Henry reactions via C-H functionalization of tertiary amines**

In this chapter, we describe the catalytic oxidation of $sp^3$ C-H bond adjacent to nitrogen of tertiary amines and nitroalkanes via CDC method to form two C($sp^3$)- C($sp^3$) bond. To effect this strategy we employ catalytic amount of $V_2O_5$ and 5 equiv of nitroalkanes using molecular oxygen as the oxidant. Moreover, the reactions are performed under neat reaction condition at 60 °C. The same reaction can be performed under aqueous media using only 2 equivalents of nitroalkanes. Tertiary amines such as *N*-aryl tetrahydroisoquinolines and *N,N*-dimethylaniline undergo facile coupling with nitroalkanes such as nitromethane and nitroethane to furnish corresponding *β*-nitroamines.[7]

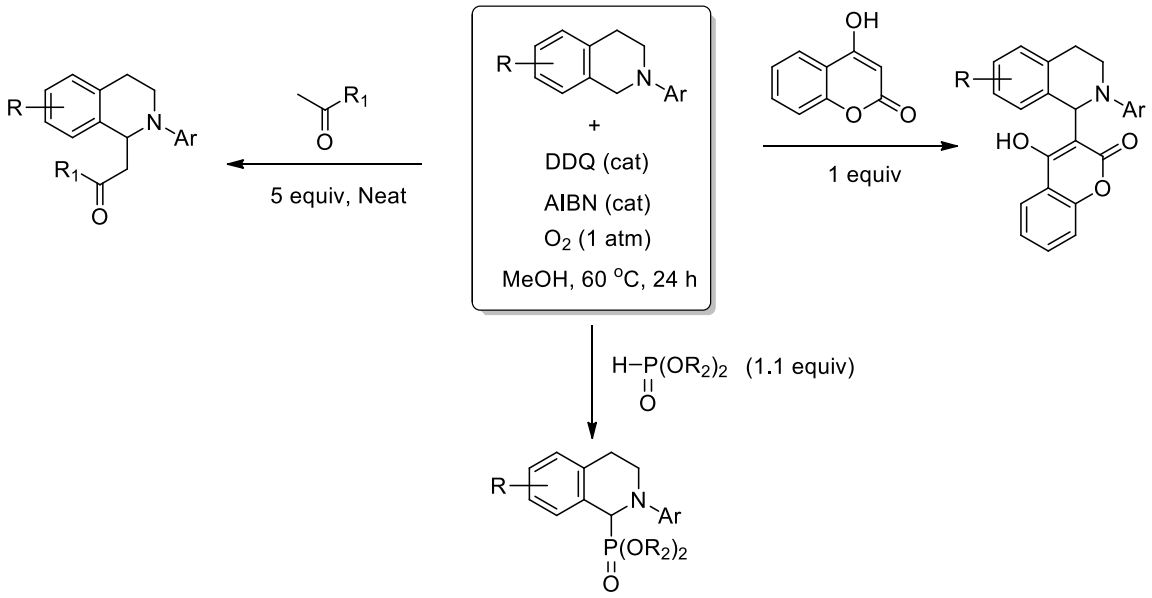
***Scheme 4.*** **Aza-Henry reactions via C-H functionalization of tertiary amines**




## Chapter 2: DDQ catalyzed cross-dehydrogenative coupling under aerobic condition: *α*-Functionalization of *N*-aryl tetrahydroisoquinolines

In this chapter, we have shown a metal-free cross-dehydrogenative coupling reaction of *N*-aryl tetrahydroisoquinolines with nucleophiles such as hydroxycoumarins, ketones and dialkyl H-phosphites. Generally, quinone oxidants such as DDQ or chloronil are employed in stoichiometric amount with or without metals for a variety of transformations. As a consequence, it is tedious to remove concomitant by-products, hydroquinones. However, utility of DDQ in catalytic amount and *in situ* regeneration of DDQ using external oxidant is scarce.[7a] C-H functionalization of $sp^3$ C-H bond of tertiary amines and ethers by CDC reaction are documented using stoichiometric amount of DDQ. However, to the best of our knowledge catalytic amount of DDQ mediated CDC reactions in the presence of molecular oxygen are not known. Herein, we describe oxidative CDC reaction of *N*-aryl tetrahydroisoquinolines with hydroxycoumarins using catalytic amount of DDQ in the presence of molecular oxygen as an oxidant and AIBN (radical initiator) as the additive. CDC coupling of *N*-aryl tetrahydroisoquinolines with various nucleophiles such as ketones and dialkyl H-phosphonates is also accomplished using this method.[8]

***Scheme 5.*** **DDQ catalyzed CDC reaction for α-functionalization of *N*-aryl tetrahydroisoquinolines**

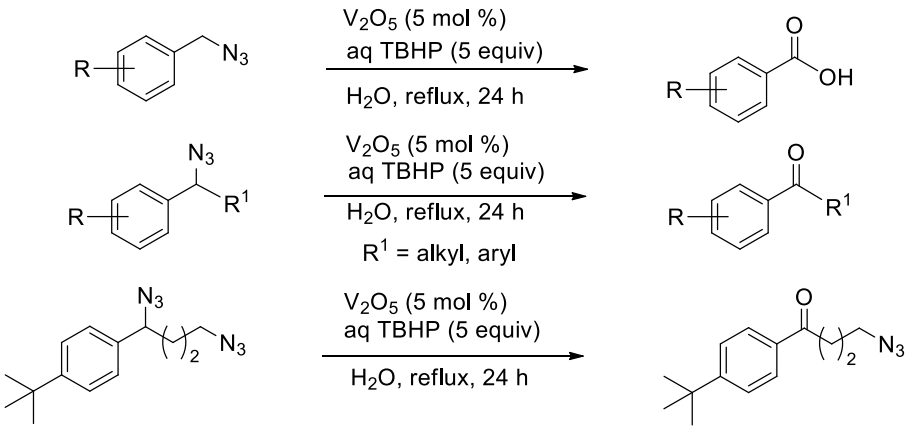



**Chapter 3** reveals the oxidation of azides and alcohols catalyzed by vanadium reagents in aqueous medium using aq TBHP (*tert*-butyl hydroperoxide) as an oxidant.

**Chapter 3: Part 1: Efficient synthesis of carbonyl compounds: oxidation of azides catalyzed by vanadium pentoxide in water using tert-butylhydroperoxide:**

In this chapter we describe vanadium-mediated oxidation of benzylic azides to carbonyl compounds in aqueous media using aq TBHP as the oxidant. Primary benzylic azides undergo facile oxidation to furnish carboxylic acids and secondary benzylic azides to corresponding ketones using $V_2O_5$ (5 mol %) as the catalyst and aq TBHP (5 equiv) as the oxidant. This strategy is applicable for selective oxidation of benzylic azides in the presence of aliphatic azides.[9]

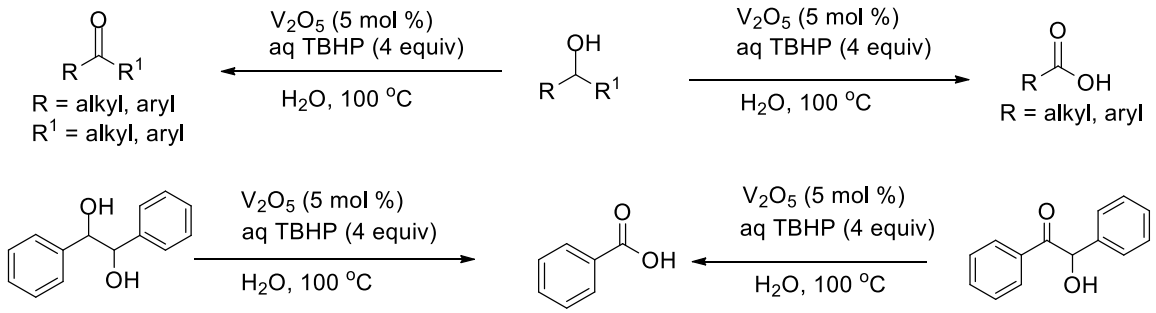
***Scheme 6. Oxidation of azides to carbonyl compounds by $V_2O_5$ in water using TBHP***




**Chapter 3: Part 2: Vanadium-mediated oxidation of alcohols to carbonyl compounds with *TBHP***

In this chapter, $V_2O_5$ mediated oxidation of alcohols to carbonyl compounds in aqueous medium using aq TBHP (4 equiv) as the oxidant is described. Primary alcohols are oxidized to carboxylic acids, whereas secondary alcohols are oxidized to corresponding ketones. However, 1,2-diols and $\alpha$-hydroxyketones undergo C-C bond cleavage to furnish the corresponding carboxylic acids.[9]

***Scheme 7. Oxidation of alcohols to carbonyl compounds by $V_2O_5$ in water using TBHP***

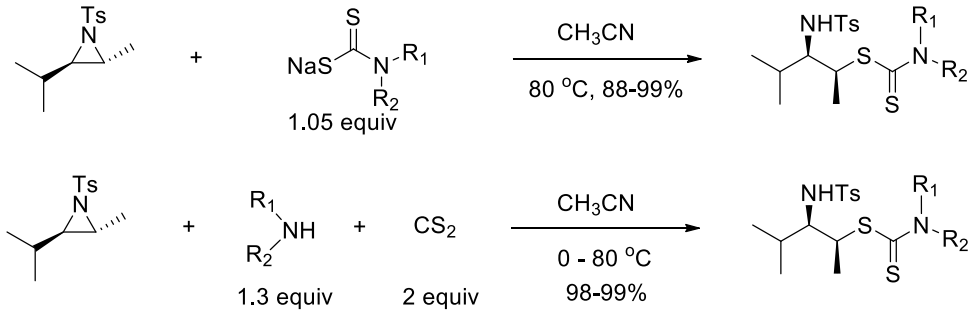



**Chapter 4: Catalyst-free regio- and stereospecific synthesis of *β*-sulfonamido dithiocarbamates: Efficient ring-opening reaction of *N*-tosyl aziridines by dialkyldithiocarbamates**

In this chapter, we have demonstrated an efficient protocol for the synthesis of *β*-sulfonamido dithiocarbamates by using a ring-opening strategy of *N*-Tosyl aziridnes by dialkyldithiocarbamates in the absence of catalyst. This strategy provides an elegant method for synthesizing a wide range of *β*-sulfonamido dithiocarbamates by using

inexpensive and readily available starting materials. As expected, most of the nucleophiles undergo ring-opening reactions at less hindered side of aziridine. In addition, a one-pot method has been developed for a facile ring opening of *N*-Tosyl aziridines by using in situ generated dialkyldithiocarbamates. These methods avoid toxic catalysts and, in most cases, give nearly quantitative yields without any byproducts.[10]

***Scheme 8. Catalyst-free ring-opening reaction of N-tosyl aziridines by dialkyldithiocarbamates***




## References

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